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Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort

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Summary
Comorbidities, are common in COPD, have been associated with poor outcomes and are thought to relate to systemic inflammation. To investigate comorbidities in relation to systemic inflammation and outcomes we recorded comorbidities in a well characterized cohort

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pulmonary disease;
Cigarette smoking;
Diabetes;
Emphysema;
Osteoporosis

(ECLIPSE study) for 2164 clinically stable COPD subjects, 337 smokers and 245 non-smokers with normal lung function.

COPD patients had a higher prevalence of osteoporosis, anxiety/panic attacks, heart trouble, heart attack, and heart failure, than smokers or nonsmokers. Heart failure (Hazard Ratio [HR] 1.9, 95% Confidence Interval [CI] 1.3—2.9), ischemic heart disease (HR 1.5, 95% CI 1.1—2.0), heart disease (HR 1.5, 95% CI 1.2—2.0), and diabetes (HR 1.7, 95% CI 1.2—2.4) had increased odds of mortality when coexistent with COPD. Multiple comorbidities had accumulative effect on mortality. COPD and cardiovascular disease was associated with poorer quality of life, higher MRC dyspnea scores, reduced 6MWD, higher BODE index scores. Osteoporosis, hypertension and diabetes were associated with higher MRC dyspnea scores and reduced 6MWD. Higher blood concentrations of fibrinogen, IL-6 and IL-8 levels occurred in those with heart disease.

Comorbidity is associated with poor clinical outcomes in COPD. The comorbidities of heart disease, hypertension and diabetes are associated with increased systemic inflammation.

Introduction

COPD is a preventable and treatable condition[1] which is often associated with comorbid conditions such as cardiovascular[2—4] and cerebrovascular disease,[5] osteoporosis,[6] depression,[7] lung cancer[8] and diabetes.[9] Population studies investigating the prevalence of cardiovascular disease, stroke, diabetes and hypertension in the COPD population conclude that these conditions are more likely to co-exist with COPD than in the general population.[10] However, the prevalence of individual comorbidities varies widely between different studies.

Comorbidities in COPD patients have a direct impact on the clinical course of the disease since they are associated with an increased risk of hospitalization and death[10—12] as well as with an increased cost of care in COPD[13,14] but despite this they are often under-diagnosed and undertreated.[15,16]

Whether or not comorbidities are pathogenically linked to the pulmonary abnormalities that characterize COPD or merely represent the co-existence of several, prevalent, age-related diseases is unclear. Since most comorbidities are characterized by low-grade chronic systemic inflammation, it has been hypothesized that chronic systemic inflammation may be a key factor linking COPD with its comorbidities.[17,18] ECLIPSE is a large observational cohort study of subjects with COPD and smokers and non-smokers with normal lung function, conducted at 46 centers in 12 countries that aimed to define distinct COPD phenotypes and identify biomarkers and/or genetic parameters that predict disease progression.[19,20] ECLIPSE therefore provides the opportunity to investigate in more detail the role of comorbidities in COPD. Using data from the ECLIPSE cohort we aimed (i) to establish the type and the proportion of patients with comorbidities in this COPD cohort compared to smokers and non-smokers with normal lung function; and (ii) to explore the characteristics of COPD patients with these comorbidities in relation to systemic inflammation and clinical outcome measures. Our hypothesis was that comorbidities would be associated with poor clinical outcomes and increased systemic inflammation.

Methods

Study design

The study design of ECLIPSE (Clinicaltrials.gov identifier NCT00292552; GSK study code SCO104960) has been published previously.[19] In brief, ECLIPSE is an observational, longitudinal study in which, after the baseline visit, participants were evaluated at 3 months, 6 months and then every 6 months for 3 years. Results presented here represent the cross-sectional analysis of the data obtained at baseline and after 1060 days follow up.

Study cohorts

2164 COPD patients (GOLD stage II—IV), 337 smokers (smokers) and 245 non-smokers (non-smokers) with normal lung function were included in ECLIPSE (Table 1). Inclusion criteria were[19]: COPD patients: (1) male/female subjects aged 40—75 years; (2) baseline post-bronchodilator FEV_1 $<80\%$ of the reference value and $FEV_1/FVC \leq 0.7$; and, (3) current or ex-smokers with a smoking history of ≥ 10 pack years. Smokers: (1) male/female subjects aged 40—75 years who were free from significant lung disease as determined by history, physical examination and screening investigation; (2) baseline post-bronchodilator $FEV_1 > 85\%$ of the reference value and $FEV_1/FVC > 0.7$; and (3) current or ex-smokers with a smoking history of ≥ 10 pack years. Non-smokers: (1) male/female subjects aged 40—75 years who were free from significant lung disease as determined by history, physical examination and screening investigation; (2) baseline post-bronchodilator $FEV_1 > 85\%$ of the reference value and $FEV_1/FVC > 0.7$; and (3) smoking history of <1 pack year. All participants signed and dated their written informed consent prior to participation (which had been approved by the ethics committees of all participating institutions); all subjects had to have the ability to comply with the requirements of the protocol and be available for study visits over 3 years. Key exclusion criteria were the presence of a respiratory disorder other than COPD. Subjects with comorbidities were not excluded but had to be

Table 1 Baseline characteristics of COPD subjects compared to healthy smoking and non-smoking control subjects. Data are presented as mean ± SD or proportion of the main clinical and functional variables as previously reported.[20]

	COPD (n = 2164)	Smokers (n = 337)	Non-smokers (n = 245)	p Value
Clinical data				
Age, years	63.4 ± 7.1[a,b,d]	55.4 ± 9.0	54.1 ± 9.0	<0.001
Male, %	65	55[c]	38	<0.001
Pack-years	48.6 ± 27.1[a,b,d]	31.6 ± 21.5[d]	0.2 ± 1.1	<0.001
Current Smokers, %	36[a,d]	61[d]	0	<0.001
BMI, kg/m^2	26.5 ± 5.7[b]	26.8 ± 4.6[c]	27.7 ± 5.4	0.002
FFMI, kg/m^2	17.2 ± 2.8[b]	17.1 ± 2.6[c]	17.2 ± 2.7	0.0.002
mMRC Score	1.7 ± 1.1[a,b,d]	0.2 ± 0.5	0.1 ± 0.3	<0.001
SGRQ-C total score	50.1 ± 20.3[a,b]	9.6 ± 12.3[c]	4.8 ± 6.5	<0.001
FEV_1, % predicted	48.3 ± 15.8[a,b]	108.6 ± 12.0[c]	114.8 ± 13.9	<0.001
FEV_1/FVC, %	44.8 ± 11.6[a,b]	79.2 ± 5.2	81.1 ± 5.2	<0.001
FEV_1 reversibility, %	10.7 ± 13.7[a,b]	4.5 ± 5.8	2.7 ± 4.5	<0.001
Distance walked (meters)	369 ± 122			
BODE index	3.2 ± 2.1			
Emphysema, %	17.7 ± 12.3[a,b]	2.4 ± 3.1[c]	4.1 ± 4.2	<0.001
Number of exacerbations[‡]	0.8 ± 1.2[a,b]	0.0 ± 0.1	0.0 ± 0.0	<0.001
Death during 1060 days follow up, %	10[a,b,d]	<1	<1	<0.001

[a] $p < 0.05$ COPD vs. smokers.
[b] $p < 0.05$ COPD vs. non-smokers.
[c] $p < 0.01$ smokers vs. non-smokers.
[d] In the year prior to study entry.

clinically stable at the time of assessment, in particular subjects with rheumatoid arthritis and inflammatory bowel disease that was active at recruitment were excluded. Patients who had an exacerbation of COPD within 4 weeks of enrollment were also excluded.[19] COPD patients were recruited from the outpatient clinics of the participating centers. Smoker and non-smoker controls were recruited through databases at these sites and other methods (advertisements in local newspaper and television/radio stations) as appropriate. Baseline characteristics of the cohorts have previously been reported.[20]

Measurements

The American Thoracic Society-Division of Lung Diseases (ATS-DLD-78) questionnaire, the modified Medical Research Questionnaire (mMRC) and the COPD-specific version of the St. George's Respiratory Questionnaire (SGRQ-C) were used to record clinical data. Exacerbations requiring treatment with antibiotics, oral corticosteroids and/or hospitalization (moderate/severe exacerbations) in the year prior to the study were also recorded. Comorbidities were self-reported using the ATS-DLD-78 questionnaire. Nutritional status was assessed by the body mass index (BMI) and fat-free mass index (FFMI) determined from bioelectrical impedance. Spirometry and the 6-min walking distance (6MWD) were performed according to international guidelines.[21,22] Spirometric reference values were those of the European Community for Coal and Steel (ECCS).[23] The BODE index was calculated according to Celli et al.[24]

All subjects underwent a low-dose computed tomography (CT) scan of the chest acquired using multi-detector-row CT scanners (GE Healthcare or Siemens Healthcare) with a minimum of 4 rows, obtained in the supine position, at suspended full inspiration, without administration of intravenous contrast. Exposure settings were 120 kVp and 40 mAs and images were reconstructed using 1.0 mm (Siemens) or 1.25 mm (GE) contiguous slices and a low spatial frequency reconstruction algorithm (GE: Standard; Siemens: b35f). CT scanners were calibrated regularly using industry and institutional standards. All of the CT scans were evaluated at the central imaging unit at the University of British Columbia, Vancouver. Quantitative assessment of the percentage of low attenuation areas (%LAA), representing the presence of emphysema, was performed using a threshold of −950 Hounsfield units (VIDA Diagnostics, Iowa City, IA, USA).

Peripheral venous blood was collected into Vacutainer tubes, in the morning, after fasting overnight, at baseline and at all visits. Circulating white blood cell (WBC) count was measured at each participating center. Serum was prepared by centrifugation of whole blood at 1500 g for 10−15 min and plasma (EDTA as the anticoagulant) was obtained by centrifugation at 2000 g for 10−15 min. Samples were stored at −80 °C until analyzed centrally. IL-6, IL-8 and TNF-α serum concentrations were determined by validated immunoassays (SearchLight Array Technology, Thermo Fisher Scientific, and Rockford, IL, USA). Serum SP-D was measured using a colorimetric sandwich immunoassay method (BioVendor, Heidelberg, Germany). PARC/CCL-18 levels were measured using a human CCL18/PARC DuoSet ELISA kit (R&D systems). High-sensitivity C-reactive protein (hs-CRP) (Roche Diagnostics, Mannheim, Germany) and fibrinogen (K-ASSAY fibrinogen test, Kamiya Biomedical Co., Seattle, WA, USA) levels were measured using immunoturbidometric assays validated for use with EDTA plasma.

Statistical analysis

Results are shown as mean ± SD, median [interquartile range, IQR], or percentage, as appropriate. Analyses of variance or van Elteren tests were used to analyze differences for continuous variables. Differences in categorical variables were assessed using Cochran–Mantel–Haenszel tests. *P* values for comparisons between cohorts (COPD Subjects, Smoker Controls, and Non-smoker Controls) were adjusted for age and gender, while *p* values for comparisons within COPD subjects were adjusted for age, gender, and smoking pack year history. Survival curves were constructed from Cox proportional hazard models that included terms for age, gender, and smoking pack year history. Additionally, hazard ratios (HR) are presented from the same models. Odds ratios from logistic regression models that adjusted for age, gender, and smoking pack year history are also calculated. *P* values less than 0.05 (two sided) were considered significant. No adjustments for multiple comparisons were done. All analyses were conducted with SAS® Version 9.1 (Cary, NC).

Role of the funding source

The study was sponsored by GlaxoSmithKline. A Steering Committee and a Scientific Committee comprising in total ten academics and six representatives of the sponsor developed the original study design and concept, the plan for the current analyses, approved the statistical plan, had full access to the data and was responsible for decisions with regard to publication. The study sponsor did not place any restrictions with regard to statements made in the final paper.

Results

2164 COPD subjects, 337 smokers and 245 non-smokers with normal lung function controls were recruited as part of the ECLIPSE study, as previously reported.[19,20] Table 1 shows the baseline characteristics of the COPD subjects compared with smokers and non-smokers. The smokers were slightly younger than COPD subjects and had lower pack years smoking history. The non-smokers had a higher BMI and a higher FFMI than COPD subjects and the smokers. As expected, COPD subjects had higher modified MRC dyspnea scores, and SGRQ-C scores than the smokers or non-smokers. Six minute walking distance and BODE index scores were determined for COPD subjects, but not for the smokers or non − smokers. By definition COPD subjects had chronic airflow limitation, whereas smokers and non-smokers had normal spirometry. COPD subjects had significantly greater %LAA on CT analysis and a significantly higher mortality during the 1060-day follow up period (Table 1).

Proportion and types of comorbidities in the COPD cohort

Fig. 1 shows the prevalence of general comorbidities. Compared with smokers and non-smokers, COPD subjects had a higher prevalence of self-reported osteoporosis, anxiety/panic attacks, peptic ulcer disease, depression requiring treatment, and diabetes, although the latter did not reach statistical significance after adjustment for age and gender. Osteoarthritis, inflammatory bowel disorder and rheumatoid arthritis were not more prevalent in COPD subjects compared with smokers or non-smokers. Peptic ulcer, reflux/heartburn and depression requiring treatment had a higher prevalence in COPD subjects than in non-smoking subjects. Anemia was more common in non-smokers than in COPD subjects. Cardiovascular comorbidities including hypertension, heart attack, heart failure, arrhythmia, and stroke and heart trouble were all more common in COPD subjects than smokers or non-smokers; however, the differences in angina, stroke, arrhythmia,

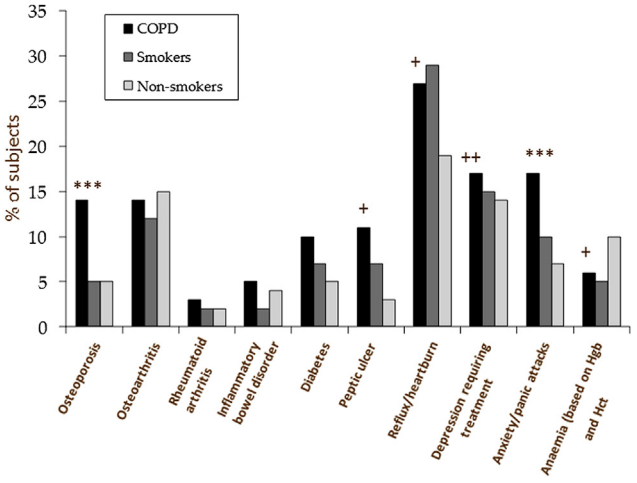

Figure 1 Percentage of COPD subjects, smokers and non-smokers with general comorbidities − ***$P < 0.001$ comparing COPD with smokers and non-smokers; ++ $p < 0.01$, +$p < 0.05$ comparing COPD with control non-smokers (*p* values adjusted for age and gender).

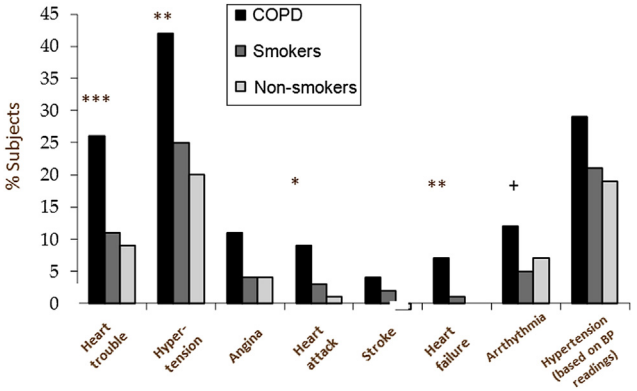

Figure 2 Percentage of COPD subjects, smokers and non-smokers with cardiovascular comorbidities − ***$p < 0.01$, **$p < 001$, *$p < 0.05$ comparing COPD with control smokers and non-smokers; +$p < 0.05$ comparing COPD with smokers (*p* values adjusted for age and gender).

and treated hypertension were not significant after adjusting for age and gender (Fig. 2).

Figs. 3 and 4 show that the proportion of patients with most of the comorbidities did not change significantly with increasing severity of airflow limitation (GOLD stage) except for osteoporosis, inflammatory bowel disease which were greater in GOLD Stage IV compared with GOLD Stage III, and anxiety/panic attacks which was more common in GOLD Stage IV compared with GOLD stage III, hypertension and angina were more common in GOLD stage II subjects compared with subjects with GOLD Stage IV.

Clinical characteristics of comorbidities in COPD

Table 2 compares the clinical, physiological, imaging, and inflammatory marker data in COPD subjects at baseline according to the presence/absence of heart trouble, hypertension, osteoporosis, or diabetes. In general, patients with any of these four comorbidities tended to be older, be more breathless, and have a lower exercise capacity, even after accounting for differences in age, gender, and smoking pack year history. Despite some statistically significant differences, overall the severity of airflow limitation was largely independent of the presence of these comorbidities (Table 2). Patients with heart trouble, diabetes and hypertension had higher BMI and FFMI than those without these comorbidities, whereas patients with osteoporosis had lower BMI and FFMI.

The extent of low attenuation areas in the lungs (emphysema as measured by %LAA) was less in those patients with heart trouble, hypertension, and diabetes, but greater in patients with osteoporosis than in those without these comorbidities (Table 2).

COPD subjects with heart trouble, hypertension, and diabetes had elevated serum levels of fibrinogen, CRP, IL-6, IL-8, CCL-18, CC16 and CRP; however, only fibrinogen, IL-6, IL-8 in those with heart trouble, and fibrinogen in those with hypertension remained significantly different after adjustment for age, gender, and smoking pack year history differences.

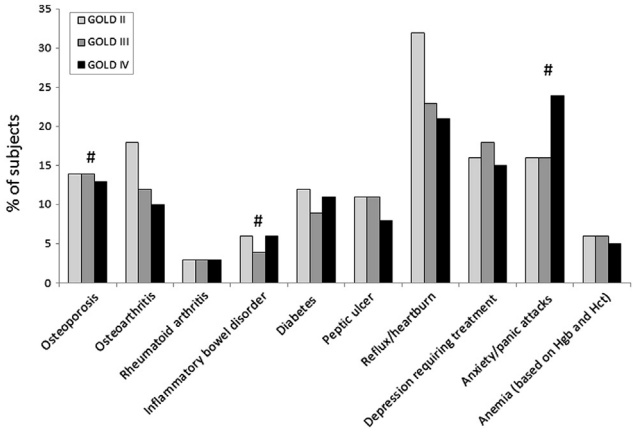

Figure 3 Percentage of COPD subjects with general comorbidities by GOLD stage of disease #$p < 0.05$ GOLD GOLD III Vs GOLD IV (p values adjusted for age, gender and smoking).

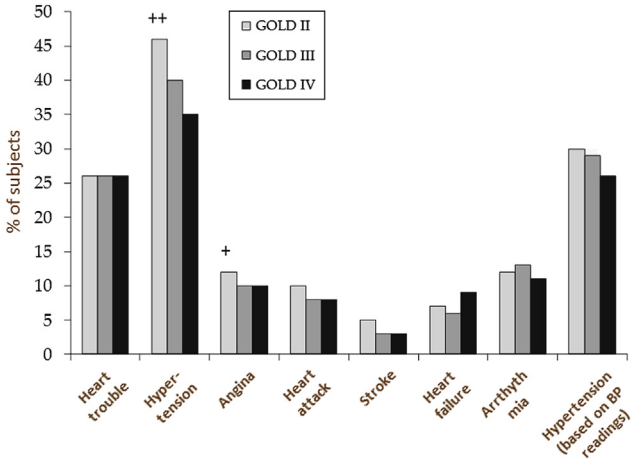

Figure 4 Percentage of COPD subjects with cardiovascular comorbitities by GOLD stage of disease − $+p < 0.05$, $++p < 0.01$ GOLD II vs GOLD IV (p values adjusted for age, gender and smoking).

Effect of comorbidities on outcomes in COPD

The effect of comorbidity on mortality in COPD was assessed over a 1060-day follow-up period adjusted for age, gender, and smoking pack year history. When co-existing with COPD, heart trouble (HR 1.5, 95% CI 1.1—2.0), heart failure (HR 1.9, 95% CI 1.3—2.9), ischemic heart disease (HR 1.5, 95% CI 1.1—2.0), heart disease (HR 1.5, 95% CI 1.2—2.0), and diabetes (HR 1.7, 95% CI 1.2—2.4) were all associated with significantly increased mortality. Neither of the hazard ratios associated with hypertension and osteoporosis, for mortality in COPD patients, were significantly different from unity. Fig. 5 presents the survival curves in COPD patients with or without heart trouble, hypertension, osteoporosis or diabetes using a Cox proportional hazard model, adjusting the data for age, gender and smoking pack year history. In this analysis the survival for COPD subjects with heart trouble or diabetes was worse than those without these comorbidities.

The number of comorbidities was also associated with increased mortality (Table 3). The hazard ratio for mortality for each additional comorbidity was 1.2 (95%CI 1.1—1.4). The presence of any of these comorbidities was not associated with decline in FEV_1, change in SGRQ, change in BODE index, or change in BMI, nor with exacerbation frequency (Table 2).

Discussion

This study shows that COPD is associated with increased comorbidities compared with smoker or nonsmoker subjects with normal lung function after adjusting for age and gender. Comorbidity was generally not associated with the severity of the airflow limitation (GOLD stage). Cardiovascular comorbidity and diabetes were associated with increased mortality and higher levels for some markers of systemic inflammation. The cumulative number of comorbidities was significantly associated with increased

Table 2 Comparison of the pattern of clinical, physiological, imaging and inflammatory data in COPD patients at baseline, and relevant outcomes at 3-year follow-up, according to the presence or absence of self-reported heart trouble, hypertension, osteoporosis or diabetes at recruitment into ECLIPSE. Data are presented as mean ± SD, median ± IQR (for biomarkers) or frequency (percentage), and a color code is used to highlight differences and similarities between patterns (red = worse; green = better; white = neutral). For further explanations, see text. □ *p* values are form a Cox proportional hazards model.

	Heart trouble			Osteoporosis			Hypertension			Diabetes		
	Yes	No	p value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
N	546	1565		283	1730		865	1205		219	1897	
Clinical data												
Age, years	65.1 ± 6.9	62.8 ± 7.1	<0.001	64.4 ± 6.3	63.1 ± 7.2	<0.001	64.5 ± 6.7	62.6 ± 7.3	<0.001	65.1 ± 6.2	63.2 ± 7.2	0.002
Male, %	410 (75%)	970 (62%)	<0.001	80 (28%)	1241 (72%)	<0.001	555 (64)	786 (65)	0.147	164(75%)	1220 (64%)	0.079
Current smoker, %	173 (32%)	597 (38%)	0.777	88 (31)	640 (37)	0.120	282 (33%)	467 (39%)	0.695	66 (30%)	705 (37%)	0.595
Pack-years	50.6 ± 28.7	47.9±26.3	0.817	47 ± 25	49 ± 28	0.331	50.6 ± 29.6	46.6 ± 24.3	0.006	57 ± 33.9	47.8 ± 26.1	<0.001
BMI, kg/m2	27.4 ± 5.7	26.2 ± 5.6	<0.001	25.6 ± 5.6	26.7 ± 5.7	0.013	28.0 ± 5.8	25.5 ± 5.4	<0.001	30.8 ± 6.1	26 ± 5.4	<0.001
FFMI, kg/m2	17.8 ±2.9	17.0 ± 2.8	<0.001	16.0 ± 2.5	17.4± 2.8	0.003	17.7 ± 2.9	16.7 ± 2.5	<0.001	19.2 ± 3.2	16.9 ± 2.7	<0.001
mMRC Score	1.9 ± 1.1	1.6 ± 1.0	<0.001	1.8 ± 1.1	1.6 ± 1.1	0.023	1.7 ± 1.1	1.6 ± 1.1	0.082	1.9 ± 1.1	1.7 ± 1.1	0.014
SGRQ-C Total Score	53.4 ± 20.3	48.8 ± 20.2	<0.001	53.1±19.0	49.1±20.5	<0.001	51 ± 20	50 ± 21	0.172	50 ± 21	50 ± 20	0.837
Physiology												
FEV1 post-bd, L	1.4 ± 0.5	1.3± 0.5	0.633	1.13±0.43	1.38±0.52	0.003	1.4 ± 0.5	1.3 ± 0.5	0.017	1.4 ± 0.5	1.3 ± 0.5	0.216
FEV1 post-bd, % ref.	49 ± 16	48 ± 16	0.309	48 ± 16	48 ± 16	0.018	49.7 ± 15.4	47 ± 16	0.002	50 ± 16	48 ± 16	0.093
6MWD, meters	351 ± 123	376 ± 120	<0.001	343±130	376±119	0.014	355 ± 115	380 ± 125	<0.001	340 ± 115	373 ± 123	0.002
Post-bronchodilator FEV1/FVC	46.3 ± 11.7	44.2 ± 11.5	<0.001	44.0 ± 10.9	44.8 ± 11.7	0.004	46.2 ± 11.6	43.7 ± 11.5	<0.001	48.2±12.9	44.3±11.4	<0.001
BODE Index	3.4 ± 2.2	3.1 ± 2.1	0.013	3.5 ± 2.2	3.1 ± 2	<0.001	3.1 ± 2	3.2 ± 2	0.270	3.3 ± 2	3.2 ± 2	0.663
Imaging												
Emphysema %	15.9 ± 11	18.3 ± 13	<0.001	21.5 ± 13	17.1 ± 12	<0.001	16.5 ± 11	18.6 ± 13	<0.001	14 ± 10	18 ± 13	<0.001
Inflammatory markers												
CRP, mg/L	3.6 ± 6.6	3.1 ± 5.5	0.308	2.6 ± 5	3.3 ± 6	0.035	3.7 ± 6.0	2.9 ± 5.5	0.142	4.0 ± 6.2	3.1 ± 5.6	0.034
Fibrinogen, mg/dL	462 ± 146	445.5 ± 123	0.001	462±135	446±126.5	0.310	462 ± 136	440.5 ± 123.5	0.042	476±125.5	446.8±129	0.067
IL-6, pg/mL	1.8 ± 2.8	1.4 ± 2.2	0.039	1.4 ± 2	1.5 ± 2	0.371	1.7 ± 2.5	1.4 ± 2.1	0.447	2.1 ± 2.8	1.5 ± 2.2	0.525
IL-8, pg/mL	7.7 ± 10	6.9 ± 9	0.005	5.4 ± 8.3	7.3 ± 10.2	0.272	6.8 ± 10	7.2 ± 10	0.602	7.6 ± 10	7.0 ± 10	0.306
TNF-alpha, pg/mL	2.4 ± 4	2.4 ± 15	0.428	2.4 ± 4	2.4 ± 10	0.994	2.4 ± 9	2.4 ± 11	0.536	2.4 ± 3	2.4 ± 10	0.508
SPD, ng/mL	121 ± 96	119 ± 86	0.868	117 ± 89	119 ± 87	0.971	116 ± 87	121 ± 90	0.602	130.1±91.9	118.9±86.3	0.914
CCL-18, ng/mL	107.7 ± 63.3	104.1 ± 51.5	0.371	108 ± 57	105 ± 53	0.954	109.6 ± 55.4	101.6± 51.2	0.885	112.7±57.1	103.9±53.5	0.108
CC-16, ng/mL	5.2 ± 3.8	4.9 ± 3.5	0.602	4.8 ± 3.6	5.0 ± 3.5	0.947	5.3 ± 3.9	4.8 ± 3.3	0.263	5.4 ± 3.9	4.9 ± 3.5	0.051
Outcomes												
Mortality □ , %	75 (14%)	127 (8%)	0.007	36 (13)	164 (9)	0.938	90 (10)	110 (9)	0.102	36(16%)	171(9%)	0.006
Exacerbation rate	0.7 ± 1.8	0.7 ± 1.7	0.662	1.3 ± 2.0	0.7 ± 1.7	0.189	0.7 ± 1.7	0.7 ± 1.7	<0.001	0.7 ± 1.7	0.7 ± 1.7	0.010
FEV1 decline	-31.3 ± 42.4	-33.8 ± 42	0.296	-31.0 ± 36.4	-33.4 ± 42.7	0.592	-31.4 ± 43.5	-33.7 ± 41.3	0.332	-30.7 ± 46.7	-33.4 ± 41.6	0.372
Change in BMI at last visit	-0.2 ± 2.1	-0.2 ± 2	0.906	-0.4 ± 2.1	-0.2 ± 2	0.295	-0.3 ± 2.2	-0.2 ± 1.9	0.519	-0.4 ± 2.5	-0.2 ± 2.0	0.092
Change in SGRQ at last visit	0.6 ± 14.6	1.2 ± 14.2	0.240	1.7 ± 13.2	0.9 ± 14.5	0.705	1.1 ± 14.1	1.0 ± 14.5	0.798	1.1 ± 14.6	1.1 ± 14.3	0.861
Change in BODE at last visit	0.5 ± 1.5	0.5 ± 1.4	0.654	0.5 ± 1.5	0.5 ± 1.4	0.649	0.4 ± 1.4	0.5 ± 1.5	0.228	0.5 ± 1.4	0.5 ± 1.5	0.764

mortality. These results have important implications for the management of the COPD population.

The type and proportion of COPD patients with comorbidities

Our findings are in agreement with recent studies showing that cardiovascular disease, diabetes, osteoporosis, gastroesophageal reflux and anxiety/panic are more common in the COPD population compared with healthy controls.[11,12] Whereas subjects with heart trouble, hypertension and diabetes had higher BMI and less emphysema, those with osteoporosis had lower BMI and more emphysema. All of these comorbidities were associated with increased breathlessness and reduced 6 min walking distance.

Comorbidity and mortality

Cardiovascular comorbidity and diabetes were associated with increased mortality in this COPD cohort after adjusting for age, gender, and smoking pack year history. The cumulative number of comorbidities was also associated with increased mortality. An association with increasing numbers of comorbidities and mortality has been reported in larger population studies.[12] Targeted treatment of comorbidities in the COPD population may therefore have an impact on outcome.

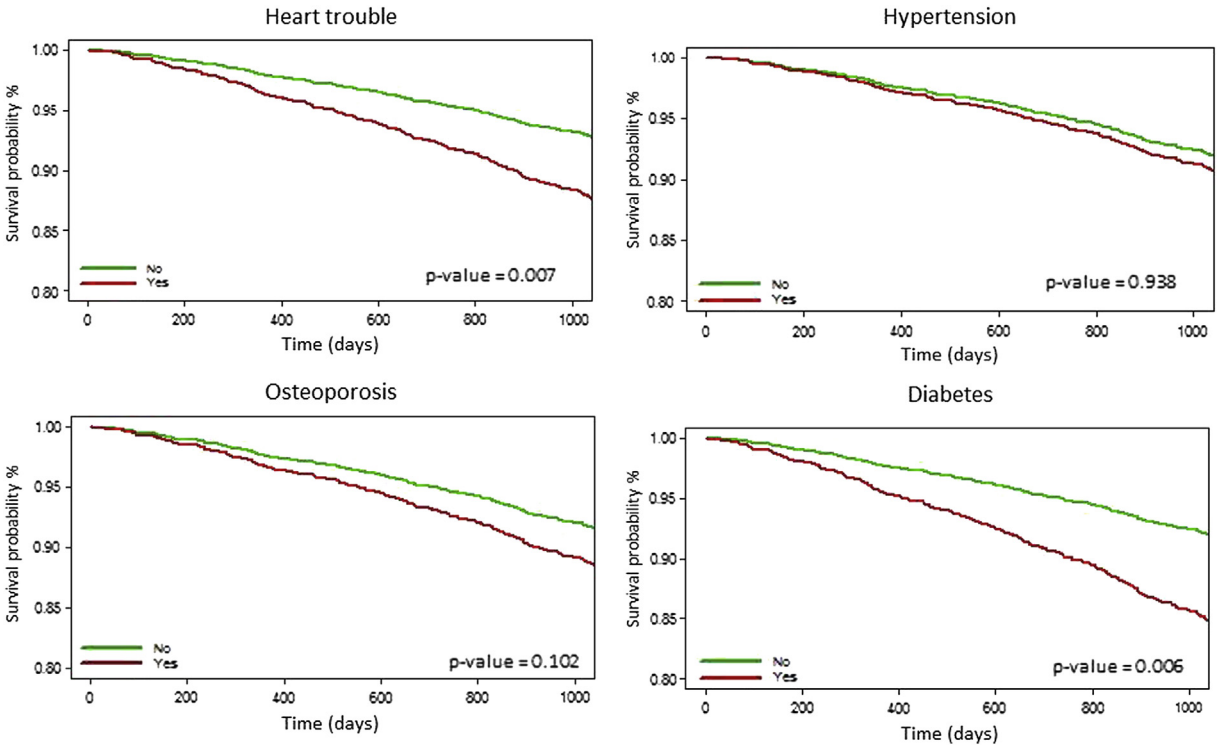

Figure 5 Survival curves in COPD with or without heart trouble, hypertension, osteoporosis or diabetes using a Cox proportional hazard model, adjusting the data for age, gender and smoking pack year history.

Inflammation and comorbidity

COPD patients with cardiovascular comorbidity had an increased level of systemic inflammatory markers compared with control subjects. Circulating fibrinogen was significantly increased in these comorbid conditions. IL-6, IL-8, fibrinogen and CCL-18 were also increased in COPD patients with heart trouble, hypertension, and diabetes, though not always significantly. A number of other inflammatory markers were altered in each of the comorbidities: hypertension was associated with increased plasma fibrinogen and diabetes was associated with higher plasma CRP. Increased systemic inflammation in COPD patients with cardiac comorbidities supports the hypothesis of systemic inflammation as a potential mechanistic link between COPD and these comorbidities. Mechanisms linking COPD with its associated comorbidities have begun to be investigated, particularly in the case of cardiovascular disease. Factors such as systemic inflammation, oxidative stress, and arterial stiffness have been reported.[25–28]

From our data, fibrinogen was increased in COPD patients in association with each of the cardiovascular comorbidities that had an impact on mortality. Elevated plasma fibrinogen has been associated with increased hospitalization rates and mortality in COPD[29] and is known to be inversely associated with FEV_1[30] and the rate of decline in FEV_1 in one previous study,[31] but not in this cohort.[32] It is interesting that C-reactive protein, which is a strong independent predictor of hospitalization and death in COPD, independent of FEV_1 and smoking history,[33,34] was associated with diabetes, but not with heart disease or hypertension. It may be that CRP and comorbidities provide complementary prognostic information in COPD.

Comorbidities should be considered as potential confounding factors in studies of inflammation in COPD. Inflammatory conditions such as inflammatory bowel disease

Table 3 Cumulative effect of comorbidity mortality in COPD using a logistic regression model adjusting for age, gender and smoking.

Number of comorbidities	Number (%) of subjects with different number of comorbidities	Number of comorbidities	Odds ratio (95% confidence interval)	*p* Value
1	1023 (37%)	1 vs 0	1.74 (1.182–2.56)	0.005
2	902 (32%)	2 vs 0	1.73 (1.131 2.64)	0.011
3	551 (20%)	3 vs 0	2.00 (1.117)	0.011
4+	211 (8%)	4+ vs 0	4.57 (2.30)	<0.001

and rheumatoid arthritis are often used as exclusion criteria in COPD studies, but not so diabetes or heart disease,[35] and yet these conditions are also associated with increased levels of inflammatory mediators common to COPD. Excluding these common comorbidities would make trial results less applicable to the COPD population as a whole.

Limitations

The COPD patients in this study comprised GOLD stage II—IV, excluding the mildest category. Thus it is therefore not possible to extrapolate results to patients with mild COPD.

Although this study investigated a large cohort of COPD patients and healthy subjects, the numbers of patients in some sub-categories were still small, which may limit the ability to generalize some of the findings. The cohorts were not ideally matched for age and smoking history although we have adjusted for these factors in the analysis.

Comorbidities were assessed by patient recall which limits the accuracy of the recorded comorbidities.

The cohort was a convenience sample of COPD patients recruited from primary and secondary care of largely moderate to severe patients with COPD. As such these patients may be more likely to have more comorbidity although we found no relationship between numbers of comorbidities and the severity of the airflow limitation.

A further limitation in our study is that smoking status was assessed by subject recall which is subject to bias and could result in differences in reported smoking in the different groups, which could have resulted in residual confounding by smoking in the analysis.

Finally, ECLIPSE was an observational study in which subjects were treated as deemed best by their clinicians. The degree by which treatment for COPD or for comorbid conditions or the duration of the disease may have influenced outcome cannot be determined from the current data set. In addition other factors such as social class and alcohol consumption could have influenced the results. However, the strength of this study was the in-depth characterization of the COPD population.

Conclusions

Comorbidities are common in COPD patients and, when present, are associated with poor clinical outcomes and increased mortality. In particular, cardiovascular disease and diabetes are associated with a poor clinical outcome in COPD patients. Comorbidities associated with increased mortality are associated with increased systemic inflammation. Increased numbers of comorbidities have a detrimental effect on outcome in COPD.

Conflict of interest

Supported by Grants from Glaxo Smith Kline (to Professors Agusti, Bakke, Calverley, Celli, Coxson, Lomas, Rennard, Silverman, Vestbo, Wouters, MacNee).

Appendix 1Principal investigators and centers participating in ECLIPSE (NCT00292552, SC0104960)

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Steering Committee: H Coxson (Canada), L Edwards (GlaxoSmithKline, USA), C Crim (GlaxoSmithKline, USA) D Lomas (UK), W MacNee (UK), E Silverman (USA), R Tal-Singer (Co-Chair, GlaxoSmithKline, USA), J Vestbo (Co-chair, Denmark), J Yates (GlaxoSmithKline, USA).

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